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Histopathology of the inner ear in patients with xeroderma pigmentosum and neurological degeneration

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Abstract

Introduction—Xeroderma pigmentosum (XP) is a rare autosomal recessive disease caused by mutations resulting in defective repair of DNA damage. XP patients have a markedly increased risk of ultraviolet induced neoplasms and premature aging of sun-exposed tissue. About 25% of XP patients in the US have neurologic abnormalities including progressive sensorineural hearing loss (SNHL).

Objective—To describe the temporal bone histopathology in two individuals with Xeroderma Pigmentosum (XPA and XPD) with neurological degeneration and to discuss the possible causes of deafness in these patients.

Methods—Temporal bones were removed at autopsy and studied using light microscopy.

Results—In the case with XPD, the organ of Corti was missing throughout the cochlea, whereas the case with XPA demonstrated scattered presence of sensory cells in the middle and apical turns. In both cases, there was moderate-to-severe patchy atrophy of the stria vascularis in all turns, and cochlear neurons were severely atrophied compared to age-matched controls, with loss of both peripheral dendrites and central axons. There was severe degeneration of Scarpa's ganglion in the case with XPA.

Conclusion—Two cases of XP with neurological degeneration are reported. The case with XPD demonstrated a more severe audiologic phenotype than XPA, although both had similar findings such as atrophy of the organ of Corti, stria vascularis and spiral ganglia leading to severe or profound SNHL by the third decade of life. It is not clear if the neuronal degeneration in the inner ear was primary or secondary to loss of neuroepithelial cells.

Introduction

Xeroderma Pigmentosum (XP) is a rare autosomal recessive disease caused by mutations resulting in defective repair of DNA damage induced by ultraviolet rays, causing premature aging of sun-exposed tissue.¹ XP was first described in 1874 by Hebra and Kaposi as a syndrome of sunlight hypersensitivity, photophobia, cutaneous pigmentary changes, and a predisposition for malignancy in sun-exposed mucocutaneous areas.² XP occurs approximately in 1 per million in Europe and the USA, and affects all races.³

Seven complementation groups for XP (XP-A to XP-G), are associated with defects in nucleotide excision repair, the process in which bulky lesions including UV photoproducts are removed from the DNA. Another form of XP (XP variant) is associated with mutations in an error-prone DNA polymerase (pol eta).¹ XP-C, XP-D and XP-A are the most common complementation groups in the USA.⁴

About 25% of XP patients demonstrate progressive neurologic abnormalities including microcephaly, diminished or absent deep tendon stretch reflexes, progressive sensorineural hearing loss (SNHL) and progressive cognitive impairment.⁴ Since the DNA damaging ultraviolet radiation (UV) in sunlight does penetrate the body to the nervous system, it has been hypothesized that the premature death of neurons in XP results from the inability to repair DNA, which has been damaged by reactive oxygen species (ROS) generated during normal metabolism.⁵ Patients with neurodegeneration have mutations in XP-A, XP-B, XP-D, XP-F, or XP-G complementation groups.¹ Nevertheless, not all patients with these mutations develop neurodegeneration.

There is scant published data describing the audiologic characterization of the SNHL and otopathology in patients with XP. Longridge⁶ described two XP patients aged 29 and 24 years with progressive, bilateral SNHL and reduced speech discrimination. The author hypothesized that the deafness was due to degeneration of central auditory pathways. Kenyon et al.⁷ reported in three XP cases a progressive downsloping SNHL with preserved speech discrimination and impaired visual suppression of the vestibuloocular reflex. Audiometric assessment suggested that the hearing loss was cochlear in origin. Robbins et al.⁸ described the temporal bone histopathology of a case of an adult XP-C patient without overt neurological degeneration that died at age 49 years. Her last audiometric test at age 48 years showed mild hearing loss for the higher frequencies, but no abnormalities were found in the inner ear. Totonchy et al.⁹ reported some of the histopathology in an XP-A patient, which will be more fully described in this paper as case 1.

The objectives of this paper are to describe the temporal bone histopathology in two individuals with xeroderma pigmentosum with neurological degeneration and to discuss the possible causes of deafness in these patients.

Case Reports

CASE 1 (XP12BE)

Clinical History—This 44 year-old white woman with a mutation in the *XPA* DNA repair gene was followed at the National Institute of Health (NIH) Clinical Center starting at age 4 years.^{4,10-15} She had more than 180 basal cell carcinomas, most of which were on her face. The patient had no squamous cell carcinomas or melanomas. She had progressive neurological degeneration, beginning with absent deep tendon reflexes noted at age 8, and progressing to truncal ataxia, inability to walk, and eventually difficulty swallowing, necessitating G-tube placement. She had global cerebral atrophy on imaging. By the age of 44 years, she became progressively unresponsive, and died when supportive measures were

withdrawn. The autopsy was performed at the NIH. Her brain was of infantile size and showed diffuse neuronal loss, myelin pallor and gliosis.^{14,15}

Otologic history—This patient developed bilateral slowly progressive SNHL beginning in the first decade of life. Audiometry at age 8 showed bilateral hearing loss of 35-40 dB HL at 8kHz.¹³ Testing at age 13 showed thresholds of 30-35 dB HL at 4 KHz and 60 dB HL at 8 KHz, but speech discrimination scores remained over 90% in both ears. Audiograms at ages 17, 19, 21, and 28 years were similar, showing a bilateral 50-70 dB HL sensorineural hearing loss for 0.25 through 8 kHz, but speech discrimination scores remained over 90% in both ears.⁹ She wore hearing aids starting at age 26 years. Audiometry at age 37 showed slight worsening of pure tone thresholds (SRT of 64 dB HL in both ears) with reduced speech discrimination scores, 64% (right) and 72% (left). Her last audiologic evaluation was at age 41, showing a bilateral downsloping pure tone loss of 65-110 dB HL, SRT of 66 dB HL in both ears, and speech discrimination scores of 52% (right) and 68% (left).⁹ (Fig. 1) Beginning in her late teens, she also began to experience difficulty in maintaining her balance. However, she did not have true vertigo.

CASE 2 (XP18BE)

Clinical History—This 45-year-old white woman with a mutation in the *XPB* gene was diagnosed with developmental delay by age 7 years and started special needs classes. The NIH Clinical Center began following her intermittently starting at age 12 years.^{4,9,12,14,15} By this time, she had photosensitivity with blistering, three skin tumors, and resection of several benign skin lesions. In contrast to Case 1, she had extensive early sun protection and did not have numerous skin cancers during her life. However, her neurologic deficits were significant. At age 31 years, examination revealed areflexia, and ataxia with a broad-based gait. She was wheelchair-bound by age 36 years. At age 40 years, she complained of decreased vision with diplopia. In April 2010, she died of respiratory arrest in the context of multiple organ failure. Her brain was of infantile size and showed diffuse neuronal loss, myelin pallor and gliosis.^{14,15}

Otologic history—This patient had a progressive SNHL first documented at age 18 that demonstrated bilateral downsloping SNHL with speech discrimination scores of 76% on the right and 80% on the left side. At age 23, her SNHL had worsened and her speech discrimination scores were estimated to be less than 20% on the right and less than 10% on the left. At age 27, her SNHL was slightly worse on the left side with no measurable speech discrimination in either ear. At age 31, she had a severe to profound SNHL in both ears with no measurable speech discrimination.⁹ A final audiogram at age 40 (Fig.1) showed a profound loss of hearing in the left and a severe-to-profound loss on the right and speech discrimination scores of 0% bilaterally.

Material and Methods

The temporal bones were removed at autopsy^{14,15} and processed for light microscopy in the standard manner, including fixation using 10% neutral buffered formalin, decalcification using ethylenediaminetetraacetic acid, embedment in celloidin, serial sectioning in the axial plane at a thickness of 20 microns and hematoxylin and eosin staining of every tenth section.¹⁶ All stained sections were examined by light microscopy. Graphic reconstruction of the cochlea was performed using the method described by Schuknecht to determine loss of the neurosensory elements including hair cells, stria vascularis, and cochlear neurons.¹⁶ (fig.1) Cochlear neuronal cell counts were compared with normative data reported by Schuknecht.¹⁶

Histopathologic findings

Case 1—The histopathology of the inner ear of this case was briefly described previously⁹ and is more fully described herein. The external auditory canal, tympanic membrane, and ossicles were unremarkable bilaterally. The mastoids were well pneumatized. The labyrinths were fully developed. The facial nerve in both ears showed reduced neuronal population. The cochleae contained 2 1/2 turns. The organ of Corti was missing throughout the basal turn and in the lower middle turn (fig.2). There was scattered loss of inner and outer hair cells in the rest of the middle and apical turns. There was moderate- to-severe patchy atrophy of the stria vascularis in all turns. There was mild apical endolymphatic hydrops. The tectorial membrane was unremarkable in all turns. Cochlear neurons were severely atrophied compared to age matched controls, with loss of both peripheral dendrites and central axons (figs. 1 and 3). The semicircular canals, the saccule and utricle were unremarkable on the left side. On the right side there was enlargement of the endolymphatic compartment of the utricle, ampulla of the superior canal and common crus. There was severe degeneration of Scarpa's ganglion bilaterally (fig.4).

Case 2—The histopathology was similar on both sides and hence is described together. The external auditory canal, tympanic membrane, and ossicles were unremarkable. The mastoids were well pneumatized. The labyrinths were fully developed. The facial nerve was normal. The cochlea contained 2 1/2 turns. The organ of Corti consisted of either a mound of cells without hair and supporting cells or a complete absence of cells (fig. 5). There was mild-to-moderate patchy atrophy of the stria vascularis in all turns. There was no endolymphatic hydrops. The tectorial membrane was unremarkable in all turns. There was severe atrophy of cochlear neurons, particularly the dendritic fibers, compared to age matched controls (figs. 1 and 5). There was degeneration of the spiral ligament. All the semicircular canals, utricle and saccule were normal, with the exception of marked reduction in the density of afferent dendrites (fig. 5, inset). The auditory and vestibular nerve trunks in the internal auditory canal had been avulsed, with only a portion of the facial nerve remaining.

Discussion

The temporal bone histopathology of 2 cases of xeroderma pigmentosum with neurological degeneration (XP-A and XP-D) was described. In both cases, the patients had progressive SNHL with a downsloping audiometric pattern, more severe in the case of the XP-D patient. Speech discrimination scores were preserved for many years, with reduction first observed at ages 37 and 18 in XP-A and XP-D, respectively. There was severe atrophy of the organ of Corti in XP-A and complete absence of sensory and supporting cells in XP-D bilaterally. In both cases there was moderate-to-severe patchy atrophy of the stria vascularis and severe degeneration of the spiral ganglion, with loss of both peripheral dendrites and central axons. There was moderate degeneration of the spiral ligament throughout the cochlea. In XP-A, there was severe degeneration of Scarpa's ganglion, whereas all the nerve trunks had been avulsed from the internal auditory canal in XP-D.

The major histopathologic correlates of the SNHL were atrophy of the organ of Corti, stria vascularis, and cochlear neurons. It is not clear whether the neuronal degeneration was primary or secondary to hair cell loss in both cases. In the XP-A patient, the initial hearing loss, characterized by pure tone threshold shifts, may have been due to dysfunction and atrophy of the hair cells and stria vascularis. However, the presence of remaining hair cells in the middle and apical turns, and the severe spiral ganglion degeneration in the XP-A case suggest primary neuronal degeneration as well. In the previously published case⁸ of an XP-C patient (XP1BE) with adult onset subclinical SNHL there was electrophysiologic evidence of a peripheral neuropathy at the age 47 years. Neuronal loss was present only in the dorsal

root ganglia. The histopathology of the temporal bones presented no abnormalities of the inner ear. The authors concluded that XP associated neurological degeneration in this adult was due to primary neuronal degeneration that manifested first in the peripheral nervous system.

Previous studies proposed the possible pathophysiology underlying hearing loss in patients with xeroderma pigmentosum.¹⁷⁻¹⁹ In addition to defects in repair of DNA damage following sunlight injury, and possibly of DNA damage caused by ROS, the *XPD* gene plays a role in transcriptional regulation. This gene is essential to life and a partial loss-of-function mutation might be expected to manifest as brain atrophy and cochlear hearing loss by faulty transcriptional events coupled with poor DNA repair.^{17,18} However, beyond DNA repair, the *XPA* gene has no other known cellular function. In 2010, Guthrie and Carrero-Martinez¹⁹ studied the expression of *XPA* mRNA in the rat in an effort to elucidate the unusual susceptibility of the cochlea to undergo degeneration in XP. They reported that *XPA* mRNA levels in the cochlea were up to 95% of the maximum expression capacity of the gene. In addition, the cochlear levels were up to threefold greater than that of the kidney, which is known to exhibit XP-DNA repair activity that is greater than most organs of the body. The authors concluded that the cochlea experiences persistent genomic stress under normal conditions, resulting in hearing loss among patients with XP. Immunohistochemistry revealed expression of *XPA* within hair cell and supporting cells of the organ of Corti, as well as in cochlear neurons, stria vascularis, and spiral ligament; these immunopositive cells are the same ones that showed atrophy in these patients' cochleae. These data suggest the neuronal degeneration might happen independently of loss of hair cells or others cells in the organ of Corti.

This previous study¹⁹ did not report on *XPA* expression within the vestibular end organs or vestibular nerve. However, the temporal bone histopathology also demonstrated severe atrophy of vestibular neurons, in addition to atrophy in the brain and cerebellum, which may have contributed to the gait imbalance.

Cockayne Syndrome is also caused by defects in DNA repair and manifests progressive SNHL of variable severity. In the first published case²⁰ a 24-year-old man demonstrated loss of the sensory and neuronal cells limited to the basal turn of the cochlea without other abnormalities in the inner ear. In a second case²¹, a 17-year-old teenager who presented with similar symptoms did not have an audiometric assessment. In a third case²², a 31-year-old man presented with a high-tone hearing loss at age 9 that progressed to total deafness at age 25 years. The otopathology in this patient showed a complete absence of the sensory epithelium of the organ of Corti, severe degeneration of the stria vascularis, and severe atrophy of spiral ganglion neurons. The vestibular maculae and cristae were atrophic in all cases. Thus other genetically induced defects in DNA repair result in similar otological findings of variable severity and may share similar mechanisms leading to hearing loss.

In conclusion, we report two cases (XP-A and XP-D) of xeroderma pigmentosum with neurological degeneration. The case with XP-D demonstrated a more severe audiologic phenotype than XPA, although both had similar findings such as atrophy of the organ of Corti, stria vascularis and spiral ganglia leading to severe or profound SNHL by the third decade of life. It is not clear if the neuronal degeneration in the inner ear was primary or secondary to loss of neuroepithelial cells.

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Fig.1.

Audiocytocochleograms of the left (A and C) and right ears (B and D) of cases 1 and 2, respectively. Graphic reconstruction of the cochlea was done in each ear using the method described by Schuknecht⁸. Black filling represents missing or abnormal elements. Vertical axes of cytocochleogram boxes for the stria vascularis and neurons represent the percentage of loss.

IHC: Inner hair cells; OHC: Outer hair cells; WRS: Word Recognition Score

Fig 2.
 (A) Photomicrograph of a mid-modiolar section of the right ear of case 1 (XPA mutation).
 Insets (B, C, D) of the apical, middle and basal turns, respectively. Some inner and outer
 hair cells remained in the apical and middle turns.

Fig. 3. Photomicrograph of Rosenthal's Canal (RC) of the right cochlea in case 1 showing severe degeneration of the spiral ganglion cells.

Fig. 4. Photomicrograph of Scarpa's ganglion (SG) of case 1 showing few remaining ganglion cells.

Fig 5. Photomicrograph of a mid-modiolar section of the right ear of case 2 (XPD mutation). (*) Asterisk shows absence of the Organ of Corti in all turns. There was atrophy of the stria vascularis and spiral ganglion. Evaluation of Scarpa's ganglion was not possible due to avulsion of the auditory and vestibular nerves; however there was marked loss of afferent vestibular neurons in sub-neuroepithelial tissues (see inset).